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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,216	12/13/1999	GRAHAM P. ALLAWAY	50875-F-PCT-	2202

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
11/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/460,216	ALLAWAY, G. P., ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination was filed on 23 August, 2007, under 37 C.F.R. § 1.114 along with the fee set forth in 37 C.F.R. § 1.17(e). Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

Claim 61 is pending in the instant application.

37 C.F.R. § 1.72

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Method of inhibiting human immunodeficiency virus type 1 (HIV-1) infection through the administration of CCR5 chemokine antagonists.

35 U.S.C. § 120 Benefit

If applicant desires to claim the benefit of prior-filed applications under 35 U.S.C. § 120, a specific reference to the prior-filed applications in compliance with 37 C.F.R. § 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. Applicants should amend the first paragraph of the specification to update the priority information set forth in the original oath/declaration. The status

of all applications (i.e., pending, patented, or abandoned) should also be updated.

37 C.F.R. § 1.98

The Information Disclosure Statement filed 23 August, 2007, has been placed in the application file and the information contained therein has been considered.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 61 is rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Simmons *et al.* (1997). Perusal of those applications relied upon for support demonstrated that U.S. Serial No. 08/831,823, filed 02 April, 1997, does not support the claimed invention. Specifically, this application failed to provide any chemokine antagonists that meet the claimed limitations. Accordingly, the instant application receives an effective filing date of 13 June, 1997, based upon the disclosure set forth in U.S. Serial No. 08/876,078. This teaching provides a RANTES analogue, aminooxypentane (AOP)-RANTES, that potently inhibited macrophage-tropic HIV-1 infection. Thus, this teaching meets all of the claimed limitations.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C.

§ 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claim 61 stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, (Fed. Cir. 1997). *Fiers v. Revel Co.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, (Fed. Cir. 1993). *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016, (Fed. Cir. 1991). *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, (Fed. Cir. 2002). *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *University of Rochester* v. *G. D. Searle & Co., Inc.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). The claim is directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a $CD4^+$ cell by contacting said cell with a **chemokine antagonist** that binds to CCR5, blocks fusion by macrophage-tropic isolates, permits fusion by T-cell-tropic isolates, and does not activate an inflammatory response.

As previously set forth, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had **possession** of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at

1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of **antagonists** that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure

of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claim of the instant application is broadly directed toward **any antagonist** that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The claims do not limit the genus to any particular type of compound (i.e., peptidyl, organic,

fatty acid, etc.) or any particular family of compounds (small molecular weight peptidyl inhibitors, antibody-based reagents, etc.). The disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. This method by itself does not lead the skilled artisan to any particular class of compounds. The disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. Thus the genus corresponding to the agent employed in the claimed assay encompasses an inordinate number of unrelated species (e.g., proteins, oligopeptides, retroinverso oligopeptides, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, small molecule inhibitors, etc.). It is noted that some data was supplied pertaining to a limited number of agents from two subgenuses. Specifically, a small number of β-chemokines were identified with inhibitory activity (e.g., the β-chemokines MIP-1α and -1β). These two chemokines are natural ligands for the CCR5 receptor. It was suggested that two chemokine antagonists, Met-RANTES and MCP-1(Δ1-8), might be useful in the claimed methodology.

Although the specification does provide a small number of inhibitory agents, nevertheless, this limited number of species are insufficient to place the inventors in possession of the full genus of agents at the time of filing. First, the disclosure fails to provide any significant structural information concerning the molecular determinants (i.e., epitopes, structural domains, etc.) on CCR5 that modulate CCR5-CD4-gp120 binding events. Thus, the skilled artisan would not be able to perform any type of rational drug-screening approach. Instead, putative antiviral agents would need to be identified through trial-and-error. Second, the disclosure fails to provide adequate guidance pertaining to the structures of any particular subgenus of inhibitory agents. The disclosure fails to provide any useful structural criteria for small molecule inhibitors, peptidomimetics, retroinverso

polypeptides, antigen-antibody binding sites, etc. Thus, the skilled artisan cannot readily envisage the structure of any particular putative antiviral agent. Third, although the specification provides a generic screening assay to identify potential candidate molecules, nevertheless, this assay fails to lead the skilled artisan to any particular subgenus of inhibitory agent. Applicants are essentially relying upon others to identify putative antiviral agents that would meet the claim limitations. Fourth, the state-of-the-art as it pertains to HIV antiviral development is characterized by unpredictability. The CCR5 chemokine receptor is a large transmembrane spanning protein. It interacts with both gp120 and CD4 during virion-cell fusion events. These interactions may employ linear domains or conformational domains. However, the precise determinants modulating these binding interactions remain to be elucidated. Accordingly, it would be difficult for the skilled artisan to identify candidate agents because of the dearth of structural information. For instance, if the skilled artisan was employing a peptidomimetic, what is the appropriate amino acid sequence of said mimetic? If the skilled artisan is going to employ a small molecule organic inhibitor, what is the structure of this compound? The disclosure fails to address these concerns. Accordingly, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed genus of compounds at the time of filing.

Response to Arguments

Applicants traverse and submit that the high level of skill in the art at the time of filing would lead the skilled artisan to conclude that applicants' were in possession of the claimed invention. The examiner is not persuaded by this argument for the reasons set forth *supra*. The disclosure simply fails to provide sufficient structural guidance pertaining to those regions of CCR5 that should be targeted for antiviral development and those classes of compounds that would be useful. Although the level of skill may

be high, it still is insufficient to put applicants in possession of the full genus of compounds.

Applicants additionally argue that a sufficient number of examples have been provided in the disclosure. The examiner acknowledges those compounds described at the beginning of the rejection. However, the specification only provides a limited number of purported antiviral compounds that function in the manner desired (e.g., Met-RANTES and MCP-1(Δ1-8)). It was further argued that a number of anti-CCR5 Mabs also inhibited macrophage-tropic binding to CCR5. However, the binding specificity, structure, and functional properties of these antibodies were not provided. Thus, it is not readily manifest if these compounds are even chemokine antagonists. For instance, these Mabs could bind to CCR5 in a region outside of the chemokine binding site, but still inhibit viral binding. Thus, they would not meet the definition of a true chemokine antagonist. In any event, once again the claims encompass an inordinate number of species which are clearly not described in the specification.

It was further argued that sufficient functional properties were disclosed to put applicants in possession of the claimed invention. This argument is not convincing since there is no correlation between any of the claimed functional properties and the structure of any given inhibitor. The applicant is basically being asked to use the screening assay disclosed to go and identify putative antivirals. This clearly does not put applicants in possession of the claimed genus.

Scope of Enablement

Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claim is directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a $CD4^+$ cell by

contacting said cell with a chemokine antagonist that binds to CCR5, blocks fusion by macrophage-tropic isolates, permits fusion by T-cell-tropic isolates, and does not activate an inflammatory response. A small number of β-chemokines were identified with inhibitory activity (e.g., the β-chemokines MIP-1α and -1β). These two chemokines are natural ligands for the CCR5 receptor. It was suggested that two chemokine antagonists, Met-RANTES and MCP-1(Δ1-8), might be useful in the claimed methodology.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claim breadth potentially encompasses a large genus of poorly defined compounds. The claim of the instant application is broadly directed toward **any antagonist** that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The claims do not limit the genus to any particular type of compound (i.e., peptidyl, organic, fatty acid, etc.) or any particular family of compounds (small molecular weight peptidyl inhibitors, antibody-based reagents, etc.). The disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. This

method by itself does not lead the skilled artisan to any particular class of compounds. The disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. Thus the genus corresponding to the agent employed in the claimed assay encompasses an inordinate number of unrelated species (e.g., proteins, oligopeptides, retroinverso oligopeptides, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, small molecule inhibitors, etc.).

2) The disclosure fails to provide a sufficient number of working embodiments. The only representative examples appear to be directed toward two chemokine antagonists, Met-RANTES and MCP-1(Δ1-8). No other working embodiments are disclosed.

3) The disclosure fails to provide sufficient structural guidance pertaining to the molecular determinants modulating chemokine antagonist binding to CCR5. Although the β-chemokines are only ~8-10 kDa, their receptors are much larger complex proteins with multiple-membrane spanning domains. In order to practice the claimed invention, the skilled artisan would require a reasonable knowledge of those determinants modulating antagonist-receptor binding interactions. However, the specification is silent concerning this topic.

4) The disclosure fails to provide sufficient structural guidance pertaining to those classes of compounds that are capable of inhibiting HIV-1 macrophage-tropic binding interactions. The claims simply rely upon a limited number of functional limitations without providing sufficient structural guidance. As set forth *supra*, the claims could potentially encompass any class of CCR5 chemokine antagonist (i.e., β-chemokine analogues, peptidomimetics, antibodies, small molecule inhibitors, etc.). However, the disclosure fails to provide sufficient guidance pertaining to those classes of compounds that can reasonably be expected to function in the recited assay.

5) Moreover, it has been well-established that the development

of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997). This is due to a number of considerations such as a failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles, despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The disclosure fails to provide sufficient guidance pertaining to the aforementioned caveats. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized

Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

12 November, 2007